

The feeding of oral poliovirus vaccine to a closed community excreting faecal viruses

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INTRODUCTION

The long-continued faecal excretion of adenoviruses in a closed community has been recently reported (Gardner, Wright & Hale, 1961) and it was considered to be of interest to re-examine the same community a year and a half later to see if adenoviruses were still being excreted. This communication presents several new features: the finding of a changing endemic virus population; the studying of the effect of oral poliovirus vaccination on these viruses; the effect of these viruses on oral poliovirus vaccine.

These have been studied in individuals (Hale, Lee & Gardner, 1961) and the effect of enteroviruses on poliovirus vaccination in large communities has been well recorded. Sabin *et al.* (1960) found that, in Mexico, 50% of the population excreted non-polio enteric viruses both before and after vaccination while Dömök, Molnár & Jancsó (1961) found that there was a rapid decrease in Coxsackie and echovirus excretion after the first oral vaccination.

Another aspect of this investigation has been to consider the general health of this community throughout the period in relation to the various adenoviruses and enteroviruses found in the stools.

The clinical significance of echovirus excretion is still incompletely understood but outbreaks of aseptic meningitis, fever, rash, respiratory infection and abdominal symptoms, especially in summer and autumn, may be associated with echovirus infections (Wright *et al.* 1961; Pelon, 1961; Ramos-Alvarez & Sabin, 1958).

INVESTIGATION

The residential home was in the grounds of a country house, in the charge of a matron. The staff consisted of qualified nurses and student nurses, most of whom were non-resident. The non-resident domestic staff were recruited locally. The length of time the children stayed in the home varied from a few weeks to many months, the latter being more usual. There were about 18 children in the home and they lived in two groups; the first group was the babies under a year old who lived in their own nursery; the second group was aged from 1 to 6 years and mixed with great freedom together. The two groups were kept separate though occasionally toddlers wandered into the nursery, and sometimes one of the older babies visited the toddlers for tea.

Faecal specimens from the children in the first 2 months of the investigation were sent twice a week and thereafter at weekly intervals. Ten per cent suspensions of faeces were made in Hanks basic salt solution containing antibiotics and 0.2 ml. were inoculated into HeLa, Hep 2 and monkey kidney tissue cells. Enteroviruses were identified by neutralization tests and adenoviruses by complement fixation as well as by neutralization (Hale *et al.* 1961; Gardner *et al.* 1961). Where there was a possibility that two enteroviruses might have been present and only one isolated, the investigation of the specimen was repeated and antiserum was incorporated to neutralize the virus already isolated in order to reveal any other virus which might have been present (Hale *et al.* 1961). This type of investigation was performed on the majority of specimens when polioviruses were being freely excreted and later on when there was evidence of reappearance of echovirus 11.

As in the previous investigation (Gardner *et al.* 1961), no attempt was made to subject the children to periodic bleeding as this would have led to the loss of confidence between children and staff which we felt was of prime importance. Since the primary interest of this investigation was the spread and the interaction of viruses in this community, the evidence could be found in faecal excretion.

All children in this home were given triple oral poliovirus vaccine at the beginning of September 1962, a second dose was given half-way through November and the third dose in mid-December. No further poliovirus vaccine was given during the remaining time of the study.

RESULTS

The endemic virus population

In the period before the feeding of the nineteen children in the home with poliovirus vaccine, that is, in the last 2 weeks of August 1962, fourteen were excreting echovirus 11 and one Coxsackie B3 virus. As soon as oral poliovirus vaccine was given, echovirus 11 completely disappeared and was replaced by the avirulent vaccine strains of poliovirus. All children in the nursery were vaccinated, but some were discharged too soon for follow-up studies. However, out of the twelve children given oral poliovirus vaccine and followed up, only one child who was 8 weeks old failed to show poliovirus excretion. He had five stools examined before vaccination and many more after; none contained virus which was detectable by tissue culture techniques.

Early in October 1962, echovirus 6 appeared for the first time and spread rapidly in the home. During October there were eighteen children in the home, of whom fifteen were excreting echovirus 6. Fourteen children arrived in the home between the first and second oral vaccinations; only two became infected with poliovirus type 2 vaccine strain which contrasted sharply with the ten children who acquired echovirus 6 infection during this period. The likelihood of infection did not vary with the age of the child and a child less than 1 year of age acquired an echovirus infection as easily as a toddler or older child.

At the end of December adenoviruses first appeared. As previously observed (Gardner *et al.* 1961) these were mainly of the non-epidemic types, i.e. 1, 2, 5 and 6.

They spread around the nursery, but did not in any way curtail the excretion of echovirus 6 which persisted well into May 1963. Adenoviruses were consistently present in the children under 1 year of age, nine out of ten being infected in comparison with three out of twelve of those over 1 year old; this was in accordance with previous observations (Gardner *et al.* 1961). Echovirus 11 reappeared at the end of February 1963 but was not widespread and did not re-infect the few remaining children who had originally been excreting echovirus 11.

There seemed to be no mutual interference between the two echoviruses and the adenoviruses, and many combinations of these viruses were found in the same stools. It appeared, too, that echovirus 6 and 11 did not exclude each other. When echovirus 6 became established in a child there was a prolonged excretion and one child so far has excreted this virus for 6 months and many other children have excreted for slightly shorter periods.

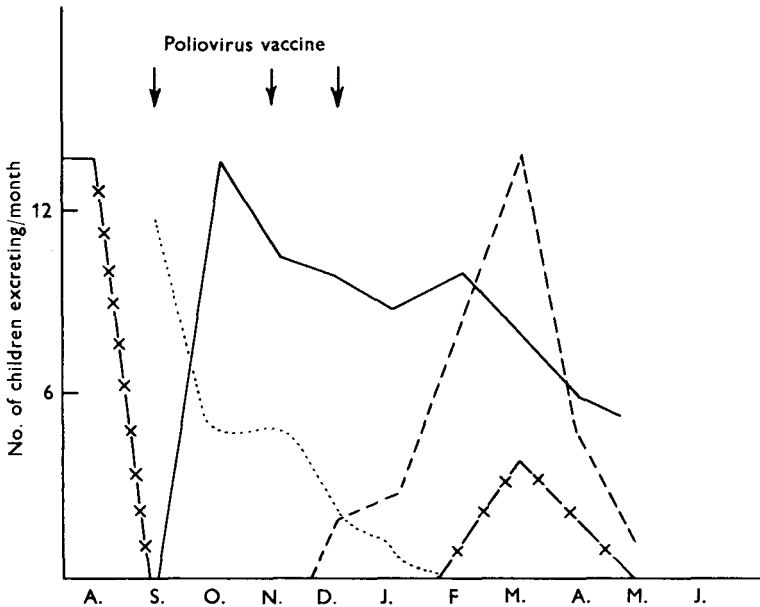


Fig. 1. Virus excretion in the residential home, August 1962–June 1963. -x-x-, Echovirus 11; —, echovirus 6;, poliovirus from vaccine; -----, non-epidemic adenovirus.

Figure 1 shows a diagrammatic representation of virus excretion in this nursery over the period of the investigation.

Clinical picture in relation to virus excretion

The children in the home were, on the whole, very well during the period under study and though there occurred an occasional coryzal and diarrhoeal episode, it bore no relationship whatsoever to the excretion of echoviruses or adenoviruses with the possible exception of one child. He developed a rash and fever which coincided exactly with the appearance of echovirus 6 in his stools which had

previously been negative. This child, too, suffered from fibrocystic disease which might account for his increased susceptibility.

There was an outbreak of chickenpox in February and March during which time a child who developed measles was admitted. It was decided to give all children over the age of four months gamma-globulin, in order to prevent the spread of measles throughout the home. The result of this was highly successful and no further cases of measles occurred. Eleven children received preventive doses of gamma-globulin but the gamma-globulin did not halt the excretion of virus already present, neither did it prevent a number of children acquiring echovirus 6 and adenovirus; one child even became infected with Coxsackie B2 virus during this period, presumably introduced from outside.

Acquisition of echovirus 6 and poliovirus by new arrivals

It was difficult to estimate how soon children, newly arrived in the home, acquired echovirus 6 infection because in some cases there was a delay of one or two weeks before the first specimen was sent to the laboratory. It was also impossible to say whether a child had brought the echovirus 6 in from outside when this virus was present in the first stool examined; this, however, was unlikely as echovirus 6 infection was not present in the general population, as judged from our concurrent surveys of normal children. If it is assumed that the echovirus 6 infections were acquired in the home, then over 80% were acquired within the first fortnight. At that time half the children were under 1 year of age and half were over a year, age making no difference to infection by echovirus 6.

Stools from a number of children were sent to the laboratory very shortly after admission. In these children it was found that echovirus 6 was acquired in a period as short as 1-5 days. The speed of acquiring infection was not related to age and infants in cots were infected in just as short a time as older children who were running about and mixing freely with their own age group. On the other hand, vaccine strains of poliovirus showed little spread around the nursery and only two children acquired these strains between the first and second vaccinations; both these infections were with the dominant type 2 poliovirus strain (Hale *et al.* 1961).

The interaction of poliovirus vaccine and the endemic viruses

Twelve children were followed up for a sufficient length of time after their first poliovirus vaccination to determine the extent of virus excretion. Table 1 shows the effect that poliovirus had on echovirus 11 which was present in the nursery before poliovirus vaccination; a child was also excreting Coxsackie B3 at the time. The child who failed to excrete poliovirus showed no evidence of being previously infected with another virus to account for this.

Table 1 shows the effect of feeding poliovirus vaccine in November and December to the new arrivals in the home; it also summarizes the effect of the second and third doses of vaccine in the presence of echovirus 6 and adenovirus excretion.

An attempt was made to estimate the length of poliovirus excretion in the home. It was found that the eleven children excreting poliovirus after feeding at the first occasion had an average excretion time of 30 days. When the children who had

primary poliovirus vaccination after the appearance of echovirus 6 and adenovirus in the home were examined for length of virus excretion, the average excretion time of poliovirus was 10 days. This included two children who had not had an echovirus 6 infection and excreted for a much longer time than this average.

Table 1. *The effect of oral poliovirus vaccine on the excretion of echovirus and adenovirus*

Feed Month	First September	Second November		Third December		
				1st	1st	2nd	1st	2nd
Given oral poliovirus vaccine			12*	9	4	3	6	3
Excreting poliovirus more than once			11	4	1	1	2	0
Previously excreting echovirus 11			8
Previously excreting Coxsackie virus B3			1
Excreting echovirus 11 or Coxsackie virus B3 after vaccination			0
Excreting echovirus 6 both before and after vaccination			.	5	4	3	.	.
Excreting echovirus 6 or adenovirus both before and after vaccination			5	3
Previously excreted echovirus 6, and excreted poliovirus more than once			.	1	.	1	.	.
Excreted poliovirus after vaccination, with no previous echovirus 6 excretion			.	0

* More than 12 were given the first feed of poliovirus vaccine, but only 12 were followed up.

DISCUSSION

The residential home has presented a complex picture; two echoviruses, 11 and 6, and a variety of non-epidemic adenoviruses have spread freely amongst the children. Though echovirus 11 may be found without any clinical illness, it is often associated with a variety of respiratory infections, enteritis, febrile illnesses with rash and very occasional paralysis and aseptic meningitis (Philipson, 1958; Ramos-Alvarez & Sabin, 1958; Sommerville, 1958; Elvin-Lewis & Melnick, 1959). On the other hand, echovirus 6 has rarely been described without clinical symptoms. There have been many descriptions of outbreaks of viral meningitis, enteritis and encephalitis due to this virus (Sandford & Sulkin, 1959; Karzon, Barron, Winkelstein & Cohen, 1956; Davis & Melnick, 1956). A surprising feature in this nursery is that in spite of the rapid infection of new arrivals, particularly by echovirus 6, in only one instance could an illness be associated with a virus, in this case echovirus 6. In this nursery the echoviruses and adenoviruses had little clinical

significance, which was at variance with the larger similar investigation of the American Junior Village when febrile illnesses were associated with new virus infections (Bell *et al.* 1961).

The next unexpected finding was that as soon as oral poliovirus vaccine was fed to children, echovirus 11 was completely replaced. This may be an example of interference, and in our experience here (Pal, McQuillin & Gardner, 1963) it was found that echovirus 11 was exceedingly slow growing and it is possible that the more rapidly growing poliovirus completely replaced echovirus 11 in the children's bowels.

Hale *et al.* (1961), showed that children who were susceptible to a particular type of poliovirus would excrete that virus. As it was not feasible in this home to employ serological techniques, the assumption was made that the children of these age groups were unlikely to be immune to all three types of poliovirus and should, therefore, excrete at least one of the types on at least one occasion. The younger the age group, the more likely they would be to excrete all three types. It was, therefore, decided to use faecal excretion of poliovirus as an index of the susceptibility of these children to poliovirus and if such excretion were absent it might be related to interference by echovirus 6 or adenovirus.

The age distribution of the twelve children given poliovirus vaccine for the first time on the first occasion was the same as the age distribution of the twelve children fed for the first time on the second and third occasions when echovirus 6 and adenovirus were present. In the first group of twelve children all except one excreted poliovirus showing that they were all susceptible. This one failure, aged 8 weeks, could not be shown to be due to a virus detectable by tissue culture techniques. Only five of the twelve children who received vaccine for the first time in November and December excreted poliovirus, and of the nine children excreting echovirus 6 before poliovirus vaccination, only two eventually excreted poliovirus (see Table 1). The difference in poliovirus excretion by the two groups is significant ($\chi^2 = 4.7$, $0.05 > P > 0.02$). It was also noted that some of those children who were excreting poliovirus during the echovirus 6 outbreak had the length of poliovirus excretion curtailed as they acquired their echovirus 6 infection. In no instance did poliovirus vaccine stop either echovirus 6 or adenovirus excretion and these viruses, if present before vaccination, were still present after.

Those children who were fed poliovirus vaccine the second time should still show some poliovirus excretion (Hale *et al.* 1961) and Table 1 shows that out of ten children only three excreted poliovirus while nine excreted echovirus 6 and adenovirus before and after vaccine feeding. These children are unlikely to be immune to all three types of poliovirus after only one feed and so this again demonstrates some interference. Table 1 shows that there is no excretion of poliovirus in those three children who were in residence long enough to receive all three feeds, and this is almost certainly due to immunity though the possibility of interference from echovirus 6 and adenovirus could not be completely eliminated. The picture that has been presented clearly demonstrates that residential nurseries and homes are not the ideal place to attempt oral poliovirus vaccination because virus interference may be an all important factor in unsuccessful immunization.

It is worth noting, too, that though mixtures of echovirus 6 and 11 with adenovirus occurred, on no occasion was poliovirus isolated from such a specimen, and in only the two instances noted did some poliovirus excretion occur after echovirus 6 excretion. Related to this problem of virus replacement was the ease with which echovirus 6 spread rapidly through the whole home, and in some cases it was apparent that children under 1 year of age and confined to their cots acquired an echovirus 6 infection in as little as 2 or 3 days. On the other hand, poliovirus vaccine strains did not spread rapidly round the home and this has been the experience of others (Hoskins *et al.* 1962). The obvious difference in infectivity of these strains might help to account for the interference picture produced by echovirus 6. As discussed previously (Gardner *et al.* 1961), the possibility of interferon production by poliovirus in the bowel might lead to suppression of other viruses and factors such as these may play a part in this very complex pattern.

Lastly, it should be noted that the giving of gamma-globulin had no effect whatsoever on the excretion of echovirus and adenoviruses, nor had it any preventive action on the acquisition of these viruses.

SUMMARY

The residential home was investigated to study the endemic virus population. During this study, oral poliovirus vaccine was given to the children and the effect of vaccination on endemic enteroviruses and adenoviruses was investigated. In the light of these findings, the problem of virus interference is discussed. The health of the children is related to their virus infections.

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